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13. ABSTRACT *(Maximum 200 words)*

Cystosarcoma phyllodes is an uncommon breast neoplasm. It is a fibroepithelial tumor composed of an epithelial and a cellular stromal component. A significant number of cases of cystosarcoma phyllodes tumors were diagnosed over the last several years at a single hospital in New Jersey.

This study is systematically assessing the epidemiology of this tumor. Initial results confirm an apparent excess of cases compared to the number expected, with a total of 97 women diagnosed with new tumors since 1987. However, the incidence of cystosarcoma phyllodes does not appear to be increased in neighboring counties. Benign cystosarcoma phyllodes tumors were found to have a significant risk of recurrence unless there are adequate surgical margins. An analytic epidemiologic case-control study will assess possible risk factors and provide guidance to future study.

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Stanley F. Weiss 9/14/95

PI - Signature Date

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RESTRICTIONS ON DISTRIBUTION

The **BODY** of this annual report includes unpublished and preliminary data. Since release of such data could compromise future publication, which is one of the technical objectives of the study, **NO PORTION** of the **BODY** should be released for distribution without specific, prior approval from the Principal Investigator.

INTRODUCTION

BACKGROUND: Cystosarcoma phyllodes tumors of the breast are uncommon breast neoplasms, accounting for about 0.5% of primary breast neoplasms[1]. These tumors are fibroepithelial tumors composed of an epithelial and a cellular stromal component. This tumor typically occurs in women from 30-69, peaking at age 40-49. In one of the largest reported case series from the United States, over a period of 78 years (1913 to 1990), 60 patients (59 women, 1 man) who were treated at the Mayo Clinic were confirmed to have cystosarcoma phyllodes tumors. This represents an average of only about one case per year. A recent study in California of malignant cystosarcoma phyllodes tumors found that the incidence rates were substantially higher in the 1980's than in the 1970's.[2] They noted that the epidemiology was strikingly different from that of the more common histologic types of breast cancer.[2]

At Englewood Hospital and Medical Center (EHMC, located in Englewood, New Jersey in Bergen County), Drs. Miguel Sanchez, Rosalyn Stahl and colleagues since 1987 noted what they suspected was a striking number of cases of cystosarcoma phyllodes tumors. This observation has served as the basis for formal and systematic investigation, as described below. The accumulation of cases of a rare tumor provides a unique opportunity to better characterize and understand unusual disease.

Some controversy exists regarding the natural history of cystosarcoma phyllodes tumors, including the risk factors for recurrence;[3-7] poor correlations appear to outnumber the studies reporting good correlations, and the unpredictable biologic behavior is noted by multiple investigators. In several of the women in our cluster, bilateral tumors have been confirmed pathologically. Several studies report the recurrence of tumors which were judged pathologically benign.[5,8,9] Thus, recognition of benign cystosarcoma phyllodes tumors is clinically relevant. Incomplete surgical excision may explain some recurrences, as the tumor may sometimes erroneously appear to the surgeon to be encapsulated. Alternatively, close surgical margins may reflect an underlying tumor biology predisposing to recurrence. The majority of patients will not experience a recurrence. Systematic analysis of natural history data regarding this tumor remains of importance. Pre-operative mammography can not differentiate cystosarcoma phyllodes from fibroadenomas.[10]

PURPOSE OF THE CURRENT WORK

The current investigation represents a collaboration between EHMC and the Department of Preventive Medicine and Community Health at the UMDNJ-New Jersey Medical School [NJMS].

The purposes of this grant in the first year were to:

- o systematically assess the occurrence of cystosarcoma phyllodes tumors at EHMC, with refinement of the preliminary data
- o assess the geographic bounds of these cases both by obtaining systematic information about these cases as well as gathering information about the occurrence of tumors at neighboring institutions
- o develop and refine primary hypotheses, study design, relevant study instruments, and begin database programming.

The purposes in the second year include completion of the initiatives begun in the first year, complemented by:

- o conducting standard epidemiologic analyses of data to characterize potential risk factors
- o summarizing findings in appropriate forums.

BODY

The differentiation of benign cystosarcoma phyllodes from benign fibroadenomas can be uncertain based on cytopathology alone,[11] so follow-up biopsy is recommended if cystosarcoma phyllodes is suspected.

We have therefore critically reviewed our data to assess what diagnostic procedures have been performed on the women tentatively identified as cystosarcoma phyllodes. In addition, the pathology material on some of the cases have been re-reviewed by the study pathologists.

Some women did not have biopsies, despite fine-needle aspirates suggestive of cystosarcoma and recommendations for follow-up. We tabulate as cases only women who have had biopsy-confirmed diagnoses of cystosarcoma phyllodes. Our data therefore will somewhat underestimate the benign cystosarcoma phyllodes tumors.

At Englewood Hospital and Medical Center (EHMC, located in Englewood, New Jersey in Bergen County), 97 women have been diagnosed with new cystosarcoma phyllodes tumors by Drs. Miguel Sanchez, Rosalyn Stahl and colleagues since 1987. An outside breast pathologist (Paul Peter Rosen, M.D., Sloan Kettering Memorial Cancer Center, New York) formally reviewed slides from a subset of the initial cases, confirming the occurrence of cystosarcoma phyllodes. New cases are continuing to be diagnosed.

Thus, this current series at EHMC is among the largest to date in the United States, representing diagnoses at a single local medical center over a relatively short period of time. The occurrence rate per year is more than 13-fold that of the Mayo Clinic series, suggesting that an unusual cluster of cases of this rare tumor has occurred in our region. Among these EHMC cases, the vast majority have been pathologically "benign": 85 benign, 1 borderline, and 11 malignant tumors. As only one case was of "borderline" pathology, and (as noted below) since it is unclear how this tumor tends to behave clinically, we have arbitrarily included this "borderline" case among the "benign" cases to simplify tabulations.

Some of our initial steps to assess these cystosarcoma phyllodes tumors have included systematization of the data in organized databases, review of pathologic material and ancillary clinical data including assessment of recurrences in terms of surgical margins as documented by pathology reports, ascertainment of continued availability of the women, and review with pathologists in neighboring New Jersey hospitals concerning tumor occurrence in their institutions.

As one approach to learn more about this unusual occurrence, we have been designing a case-control interview study. The interview is designed for telephone administration, as preliminary work

indicated that a number of women had already moved outside the local area and had not recently seen their primary care referring physician. Thus, it would be difficult logistically to meet with many of the women in person, and we wished to standardize our interview approach. Furthermore, in recent years telephone interview questionnaires were successfully utilized in studies of breast cancer conducted in Long Island, New York and in Seattle, Washington. Copies of these instruments were generously provided to Dr. Weiss, and these were extensively consulted during our pilot study development process; we are indebted to those investigators for their assistance.

Candidate cases in our initial baseline study are based on a diagnosis of cystosarcoma phyllodes at EHMC, with all diagnoses of cystosarcoma phyllodes reflecting formal review and concurrence of the study pathologists and co-investigators, Drs. Sanchez and Stahl. The attending physician who referred the subject with cystosarcoma phyllodes to Dr. Sanchez has been contacted by Dr. Sanchez. If that physician has no objection, the subject is sent a letter and subsequently called. In addition, the case's attending physicians have provided some medical history and treatment data, on a standardized abstraction form we developed. Study personnel assist the physicians with the abstraction. Women who agree to be interviewed will be sent a written consent form, to be returned by mail in a self-addressed, pre-paid envelope. The consent will also request permission to study their stored anatomic material (paraffin embedded tissue blocks at EHMC). Specimens from women who sign this consent will be used in analyses linked to their questionnaire and medical data. For women who do not sign consent, we plan to identify any sequential specimens from a single woman and abstract key categorical data (e.g., age group, type of tumor, familial history if available), to enable us to subsequently break linkage between their personal identifiers and their specimens.

The EHMC "Cytodiagnosis and Breast Care Center" [CBCC] also sees many women who do not have breast cancer, so that a regional source for control subjects is readily available. Controls for the current study phase are being chosen from among those woman <u>without</u> breast cancer who have attended the EHMC CBCC. There are some pathologic similarities between cystosarcoma phyllodes and fibroadenomas. Furthermore, one study found cytogenetic similarities between phyllodes tumors and fibroadenomas of the breast, suggesting the possibility of similar pathogenetic mechanisms in some cases.[12] This raises the theoretical possibility that both might share some common epidemiologic characteristics. If so, controls with fibroadenomas would be expected to dilute the power to detect etiologic leads. Thus, women with a history of fibroadenoma will also be excluded from the interview control group. Potential controls are being matched to cases by: a) age, approximately $\pm$ 1 year; and b) year of diagnosis, approximately $\pm$ 1 year. Initial contact is through a letter sent by Dr. Sanchez.

If a potential control declines or can not be found, a replacement control will be sought using the above matching algorithm, with this process tracked. Controls will also be sent written consent forms for signature.

The telephone interview form has been designed to maximize pre-coding and with skip patterns to minimize interview time. It has been extensively tested, and takes somewhat over one hour for cases and controls. It covers demographic information, treatment data, medical history with an emphasis on gynecologic/obstetric and hormonal/endocrine matters and events during the time period of breast development, and measures of exposure to some possible sources of environmental agents. There are detailed histories concerning residences (e.g. location, years, heating systems, water sources, pesticide use) and of both personal and spousal occupational histories. In addition, given that about a third of the women are relatively young (under age 30 when diagnosed) and the occurrence of these tumors is recent, a short latency period may be involved. We can not a priori exclude that an infectious agent might be involved, among the many possibilities. Given the significant spread of multiple sexually transmitted agents during the last two decades, some questions about sexual behavior are warranted; we have carefully tried to balance the sensitivity of this subject and the mode of interview (telephone) with the potential importance of the data in asking about sexual behavior and past disease, and have found our instrument to flow smoothly and comfortably in the telephone interviews to date. These issues are also briefly covered in the physician medical chart abstraction form we have developed. Data will generally be entered through menu-driven database software ("Q&A") with conversion to a SAS database for most statistical tabulations.

We chose to proceed with the above steps before embarking upon biologic research studies or establishing a tissue bank to ensure that these steps were warranted. We note below some intriguing molecular biology data which are relevant to the development of future laboratory-based initiatives.

Descriptive Epidemiology of Cystosarcoma Phyllodes Cases at EHMC

Most of the patients with cystosarcoma phyllodes that have been identified so far, at the time of diagnosis, were employed and resided in multiple towns, primarily in the northern New Jersey county of Bergen, which borders on upper Manhattan. However, no single localized neighborhood appears to be involved based on a tabulation of most recent address; the initial cases span over 27 zip codes (most of which are close to each other, consistent with this being a local hospital). Since some latency period must exist, a detailed examination of residential history is requisite to examine whether or not there is evidence of clustering (compared to a control group) at any point in time, which will be

accomplished by analysis of data obtained in the case-control study.

Most of the women in our study are "white-collar" workers based on hospital admission registration history. Approximately 60% of the women are married.

In our cluster of malignant and benign cystosarcoma phyllodes cases, the racial distribution is 90% caucasian (non-Hispanic). This contrasts with a recent report concerning malignant cystosarcoma phyllodes in California,[2] where most tumors occurred among Latino white women.

Temporal Pattern

The overall temporal pattern of case diagnosis, with regression analysis based on year of diagnosis among the 94 patients first diagnosed with a cystosarcoma phyllodes tumor at EHMC between 1987 and 1994, inclusive, does not demonstrate a clear pattern. Of interest, however, is that among the malignant cases there is a statistically significant, mildly positive slope ($p < .05$; SAS general linear model [SAS Institute, Inc., Cary, NC]), indicating an increasing incidence of malignant diagnoses. It is important to note that our numbers remain small.

Age Distribution

The age distribution of these women appears quite unique - many women were less than 30 y/o (benign tumors, 28/86 (33%); malignant tumors, 3/11 (27%)), with ages ranging from 16 to 69 y/o. There were no cases of juvenile fibroadenoma, a benign form of cystosarcoma phyllodes seen in adolescent women aged 11 to 15.[13] The women with malignant lesions (mean 40.3 y/o) were significantly older than those with benign tumors (mean 33.1 y/o), $p < .05$ (ANOVA).

Laterality and Recurrences

There was no evidence of laterality: 47 women had cystosarcoma tumors only in the right breast, 44 in the left breast only, and 6 had tumors bilaterally.

Six (6.2%) women have had pathologically documented recurrent tumor; these occurred solely among those with "benign" tumors, at 0.90, 0.98, 3.78, 4.14, 4.91 and 6.32 years after the initial diagnosis.

The sequence of pathology reports from the original tumor were reviewed, and margins preliminary classified as documented

"adequate surgical margin" vs. "other." Whereas only 1.5% (1/66) of tumors with adequate margin recurred, 16.1% (5/31) with "other" margins recurred (relative risk 10.6, p=.01). Recurrence rates in small published case series were 15-20% overall.[14] Thus, our overall rate is lower than in prior series. This may in part reflect the recommendations of the pathologists at EHMC to the surgeons for adequate resection margins, with the acceptance of additional surgery near the time of initial diagnosis. Our data serve to support this recommendation.

Three apparent new primary cystosarcoma tumors also occurred, at 0.66, 1.79 and 2.22 years.

The number of bilateral tumors and the occurrence of new primary tumors suggests that these women have an increased susceptibility to this tumor. Since some women had both benign and malignant tumors, our preliminary data suggest that the benign and malignant tumors may have some pathogenetic mechanisms in common. These data suggest that environmental or transmissible factors, as well as genetic factors, should be strongly considered as possible etiologic factors in a exploratory initial study.

Relevant Genetic Literature

Mutations in the p53 tumor suppressor gene[15] have been detected in about half of cases of human cancer. While the importance of this gene in respect to tumorigenesis is not in debate, the question remains what precise role these mutations have in neoplastic cell growth in view of the fact that they appear at different stages of tumor progression and the multiple effects of p53.[16] The p53 gene is located on the short arm of chromosome 17 (17p13)[17] and encodes a 53-kd nuclear phosphoprotein that functions as a negative regulator of cell proliferation. The gene is 20 kilobases and encodes a 2.8 Kb mRNA consisting of 393 amino acids. There are 11 exons, the first of which is non-coding.

Mutations of p53 have been identified in breast tumor specimens and in patients with Li-Fraumeni syndrome,[18,19] which is associated with an increased incidence of breast cancer.[20] In at least two families with p53 mutation,[21,22] including one of the initial families reported with Li-Fraumeni syndrome women had a malignant cystosarcoma phyllodes breast tumor. In immunohistochemical studies in which stabilized and/or mutant p53 was detected, altered p53 was found to be associated with poorer prognoses. Breast tumors with positive axillary lymph nodes showed a higher percentage of p53 immunoreactivity. Data derived from patients with breast cancer showed a poorer survival rate for the patients with positive p53 tumors.[23]

Potential for Laboratory Assessments

The clinical pathologic material on which the cystosarcoma phyllodes diagnosis are based, which includes paraffin embedded tissue for the women who had surgical biopsies (which is recommended for therapeutic purposes and diagnostic confirmation if a fine needle aspirate suggested the diagnosis) are stored within the Pathology Department at EHMC. These tissues are thus a valuable resource for the development of a tissue bank and potential laboratory testing. We plan to obtain written consent from as many women with cystosarcoma phyllodes tumors as possible to enable linked testing in future initiatives.

Cystosarcoma Phyllodes Tumor Occurrence at Other Institutions

We have formally contacted other institutions to gather preliminary data on the number of cases of cystosarcoma phyllodes detected at those institutions. This involves an evaluation of the ways in which diagnostic data has been recorded at each place, and the reliability of the information. The data were collected by identifying cases with cystosarcoma phyllodes from histologically confirmed pathologic reports as well as data reported by the chief pathologist at each hospital.

Data were gathered for the time period from 1986 through June 30, 1995, and classified by year, and whether benign or malignant. Thirty one hospitals were contacted, and twenty nine hospitals participated in the survey. Seven hospitals had no record of any cystosarcoma phyllodes tumor since 1986. From each hospital the yearly number of surgical pathology specimens examined (surgicals) was also obtained. The incidence rates for benign and malignant tumors were calculated separately per 100,000 surgicals per year for each hospital and summarized by year, by the last ten years, and by county. If data were not available for a given year, that hospital was excluded from the summary calculation per surgicals from both the numerator and the denominator for that year.

The number of all women in each county (1990 U.S. Census) was utilized as a preliminary denominator in calculating population-based rates. (One refinement for future calculation would be to use the number of adult women as the denominator.) Incidence rates for benign and malignant tumors were also calculated per 100,000 females per year residing in each of the studied counties. Calculated rates for 1986, 1987, 1994, and the first six months of 1995 for the sum of the malignant and benign tumor rates combined are presented for illustration and purpose of comparison.

It is important to note that the records available at many institutions are manually maintained for some or all years, and thus not amenable to systematic extraction. Data from affiliated tumor registries were felt likely by the collaborating pathologists

to include malignant cases but not necessarily benign cases. Thus, there are considerable limitations to the tabulations that can be made.

Findings

Two hospitals in Passaic county had no cases of cystosarcoma phyllodes, while three hospitals reported cases. Overall, there was an increase in the incidence rate per 100,000 surgicals of the tumor from 4.30 in 1986, 8.59 in 1987, to 7.25 in 1994 and 6.97 in the first six months of 1995. In Hudson county, nine hospitals were surveyed; three had no record of cystosarcoma phyllodes since 1986, and six hospitals had cases. There was an increase in the incidence rate from 2.64 in 1986, 0.0 in 1987, to 5.5 in 1994 and 5.5 in the first six months of 1995. Of eleven hospitals in Essex county, information could be obtained from only nine of the hospitals. Two hospitals had no cases and seven reported cases. There was an increase from 3.42 in 1986, 2.65 in 1987, to 13.34 in 1994 and 2.71 in the first six months of 1995. The three county rate over the ten year period from 1986 through 1995 was 5.17 for benign and 6.32 for malignant cystosarcoma phyllodes tumors, a total of 11.49 cystosarcoma phyllodes tumors, diagnosed per 100,000 surgicals per year.

In Bergen County, one hospital ("Hospital H") could only estimate the number of cases and the actual pathological reports were not readily retrievable. Thus, the incidence rates for Bergen county were calculated with and without Hospital H. Data was not available for 1986 from our index hospital, EHMC. Without Hospital H, the incidence rate in 1986 was 4.67 per 100,000 surgicals per year, 18.26 in 1987, 17.26 in 1994, and 22.04 for the first six months of 1995. With Hospital H, the incidence rate was 30.86 in 1986, 33.93 in 1987, 27.01 in 1994 and 27.60 in the first six months of 1995. The incidence rates per 100,000 surgicals and per million women per year (MWY) in Bergen County was compared to the overall rate in the surrounding three counties for the overall time period from 1986 through June 1995. In the three counties of Essex, Passaic and Hudson the total number of benign cases was 17, and a total female population of 930,000 giving a rate of 1.8 per MWY. In Bergen county excluding Hospital H there were 97 benign cases, an incidence rate per MWY of 22.6, significantly higher than the surrounding counties (Rate Ratio [RR] = 12.4, 95% confidence interval [CI] = 7.3-22.1). Including the additional 80 benign cases estimated by Hospital H, the total of 173 (estimated) gives an overall rate of 40.3 per MWY (RR = 22.6). For malignant tumors, there were 23 total cases in the three surrounding counties of Essex, Passaic and Hudson, for a rate of 2.4/ MWY. In Bergen county without Hospital H the incidence rate for malignant cases was 4.7 (RR = 1.9, 95% CI = 0.98-3.60) and with Hospital H 6.7 (RR = 2.7, 95% CI = 1.5-4.9).

These data reinforce the impression that clustering appears to exist in Bergen County associated with EHMC, and perhaps also at the neighboring Hospital H. These data indicate that the incidence rate of cystosarcoma phyllodes, a rare tumor of the female breast is significantly elevated in northeastern New Jersey over the time period from 1986 through 1995. The data demonstrate an apparent clustering of these rare tumors in Bergen county. The incidence rate per hospital surgicals was seven fold higher, and nine fold higher in the female population in Bergen county compared to the surrounding counties of Essex, Passaic, and Hudson.

These results may in part reflect increased diagnostic awareness of this tumor among the pathologists in Bergen County. However, considerable attention is paid to malignant diagnoses by pathologists. so malignant tumors in particular are unlikely to be missed. An increased incidence of malignant cystosaroma phyllodes is therefore less likely to be attributable purely to enhanced detection. Thus, the increased incidence of malignant cystosarcoma phyllodes tumors (and the trend towards a slight increase in incidence rate) suggests that there truly is a clustering which may be clinically important.

The known recurrence potential of benign tumors reinforces the importance of diagnosis. These results suggest that further epidemiologic study to examine potential environmental or genetic factors is warranted, so that issues of prevention and etiology can be assessed.

Summary

In summary, this first grant year has been productive. We have met the general objectives of the Year One "Statement of Work" we proposed in our original grant application, and we are well prepared to undertake Year Two. Furthermore, the initial findings support the importance of continuing this project.

CONCLUSIONS

We are developing important descriptive epidemiologic data concerning the cases of cystosarcoma, both in terms of patient profile and natural history. Of interest is the finding that the women with malignant tumors were significantly older than the women with benign tumors.

The occurrence of both benign and malignant tumors in individual women suggests the possibility that the underlying etiology of malignant and benign tumors may have similarities. Among women with benign cystosarcoma phyllodes tumors, a significant number recurred. We confirm earlier reports that adequate surgical resection is important, pointing to the need for accurate diagnosis and recognition of these tumors, including benign tumors.

The evolving data are consistent with an increased incidence of this rare tumor in the region near Englewood Hospital and Medical Center. This may in part represent enhanced diagnostic awareness of the pathology of benign cystosarcoma phyllodes tumors.

The initial findings support the plans for our conduct of an analytic case-control study. However, the number of cases limits our power, so that we anticipate only being able to detect strong risk factors; nevertheless we shall conduct rigorous analytic analyses during the second year of our grant to detect potential risk factors and assess what biologic factors should be prioritized for future study through the use of tissue repository specimens. Given our finding of intriguing, statistically significant differences in the descriptive data, we may be able to find important new information about this rare tumor.

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DEPARTMENT OF THE ARMY
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REPLY TO
ATTENTION OF:

MCMR-RMI-S (70-1y) 22 Jun 00

MEMORANDUM FOR Administrator, Defense Technical Information Center, ATTN: DTIC-OCA, 8725 John J. Kingman Road, Fort Belvoir, VA 22060-6218

SUBJECT: Request Change in Distribution Statements

1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical reports written for Award Numbers DAMD17-94-J-4423, DAMD17-94-J-4172, DAMD17-94-J-4367, and DAMD17-94-J-4187. Request the limited distribution statement for Accession Document Numbers **ADB215483, ADB234438, ADB249605, ADB225305, ADB232775** and **ADB249636** be changed to "Approved for public release; distribution unlimited." These reports should be released to the National Technical Information Service.

2. Point of contact for this request is Ms. Virginia Miller at DSN 343-7327 or by email at Virginia.Miller@det.amedd.army.mil.

FOR THE COMMANDER:

PHYLIS M. RINEHART
Deputy Chief of Staff for
Information Management